UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/990,438 | 11/14/2001 | David Botstein | 10466/201 | 2374 |

35489 7590 05/31/2006

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

| EXAMINER | |
|---|---|
| KAUFMAN, CLAIRE M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov



**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/990,438
Filing Date: November 14, 2001
Appellant(s): BOTSTEIN ET AL.

Ginger R. Dreger
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 17 April 2006 appealing from the Office action mailed 19 August 2005.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/989,328 (allowed)

09/993,687 (under appeal)

09/992,643 (under appeal)

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

No amendment after final has been filed.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because it incorrectly describes Claim 124 as specifically reciting that the PRO290 polynucleotide is amplified in human lung and colon cancers as compared to normal, non-cancerous human tissue controls (p. 2, middle of last

paragraph, of the brief). There is no such limitation in Claim 124. It is also stated at the bottom of p. 2 of the brief that "In addition, the invention also claims the amino acid sequence of the polypeptide of SEQ ID NO:33, lacking its associates signal peptide...." No claims have the limitation directed to the lack of signal peptide. Finally, the last sentence of the paragraph bridging pages 2-3 of the brief discusses Claims 140-143, however, these claims do not exist in the instant application.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Pennica et al., 1998, PNAS USA 95:14717-14722.

Konopka et al., Proc. Natl. Acad. Sci. (1986) 83:4049-4052.

Chen et al., 2002, Molecular and Cellular Proteomics 1:304-313.

Hu et al., 2003, J. of Proteome Res. 2:405-412.

Haynes et al., 1998, Electrophoresis 19:1862-1871.

Gygi et al., 1999, Mol. Cell. Biol. 19:1720-1730.

Lian et al., 2001, Blood 98:513-524.

Fessler et al., 2002, J. Biol. Chem. 277:31291-31302.

Hanna et al., 1999, Pathology Associates Medical Laboratories.

Hittleman et al., 2001, Ann. N.Y. Acad. Sci. 952:1-12.

Livak et al., 1995, PCR Methods Appl. 4 :357-362.

Sen et al., 2000, Curr. Op. Oncol. 12:82-88.

Heid et al., 1996, Genome Res. 6:986-994.

Hyman et al., 2002, Cancer Research 62:6240-6245.

**(9) Grounds of Rejection**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following ground(s) of rejection are applicable to the appealed claims:

Claims 124-125 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to isolated polypeptides comprising an amino acid of SEQ ID NO: 33, also known as PRO290, or the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209790, wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors. It is noted that the amplification in lung or colon tumors of the nucleic acid encoding the PRO299 polypeptide is not an activity of the polypeptide, but rather a characteristic of a nucleic acid. Appellants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief, p. 4, beginning of arguments. (It is noted that the specification asserts several other utilities for the claimed polypeptides, all of which have been found to be non-specific and/or insubstantial. For discussion of these utilities, see Office Action mailed 19 October 2005. However, these asserted utilities will not be re-addressed here due to Appellants' indication that they are relying upon the gene amplification assay for utility and enablement.)

At pages 539-555, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO290 had a ΔCt value of at least 1.0 for 5/11 lung tumor samples and 2/17 colon tumor samples. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 545, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." At page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit

(e.g. 1.22), and (b) that very few values were obtained that were at least 2.

While these data are pertinent to utility and enablement of PRO290 *genomic DNA* for use in lung or colon tumor diagnosis, the data have no bearing on the utility of the claimed PRO290 *polypeptides*. In order for PRO290 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels, which in turn would have to correlate with increased polypeptide levels. No data regarding PRO290 mRNA or PRO290 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between mRNA levels and polypeptide levels. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and e0xpression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state (abstract_ that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Phl template."

Moreover, even if increased mRNA levels could be established for PRO290, it does not follow that PRO290 polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304), and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples"

(pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean mRNA expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying mRNA changes of 5-fold or less in tumors compared to normal, there was no evidence of a correlation between altered mRNA expression and a known role in the disease. However, among genes with a 10-fold or more change in mRNA expression level, there was a strong and significant correlation between mRNA expression level and a published role in the disease (see discussion section).

The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. For example, Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient."

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (*e.g.*, p. 514, top of left column): "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels." Lian et al. note (p. 522, first sentence of each of last two paragraphs), "The discrepancies

between mRNA and protein levels in MPRO cells appear to be substantially larger than those observed for yeast. Possible causes for the discrepancies include translational regulation, differential expression of certain mRNAs at various stages of cell growth in vitro, post-translational protein modification that varies with the state of maturation of the cells, and selective degradation or excretion of proteins in vivo.... The initial studies of protein expression presented here provide a cautionary note for efforts to interpret cell composition and function in relation to mRNA levels." See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302), who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

Therefore, data pertaining to PRO290 genomic DNA do not indicate anything significant regarding the claimed PRO290 polypeptides. The data do not support the specification's assertion that PRO290 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO290 polypeptide is overexpressed in any cancer to the extent that it could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO290 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO290 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 124-125 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed polypeptide because no particular function or specifically associated disease has been determined for the encoding polynucleotide of SEQ ID NO:32 or encoded polypeptide of SEQ ID NO:33, and there is no disclosed definite function supported by the prior art. No function can be reasonably assigned based on its homology to another polypeptide(s). Using the claimed polypeptide would require undue experimentation.

**(10) Response to Argument**

In general, Appellants' organization of arguments will be followed.

***Appellants' Summary of Arguments***

At the middle of p. 4 of the Brief, Appellants argue that the patentable utility of PRO290 polypeptides is based on the gene amplification data for the gene encoding the PRO290 polypeptide. Appellants state that the specification shows significant amplification of the gene encoding PRO290 in several different lung and colon tumors. Appellants refer to the declaration of Dr. Goddard (submitted under 37 C.F.R. § 1.132 on 02 August 2005) as explaining that a gene that is amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful for the diagnosis of cancer, for monitoring cancer development, and/or for measuring the efficacy of cancer therapy. Appellants urge that such a gene is useful as a marker for the diagnosis of lung or colon cancer. This has been fully considered but is not found to be persuasive, as it does not address the utility of the claimed subject matter, *i.e.*, PRO290 *polypeptides*. It is maintained that the gene amplification assay does not provide a patentable utility for polypeptides because amplified genomic DNA is not predictive of increased mRNA or polypeptide levels, for reasons discussed herein. For example, the art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide levels (*e.g.,* Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al.). Since the instant claims are directed to polypeptides, this is a major concern. The Goddard declaration was not found to be sufficient to overcome the rejection; however, the Goddard declaration will be addressed at length later in this answer.

At the bottom of p. 4 to the middle of p. 5 of the Brief, Appellants argue that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide is also expressed at an elevated level. Appellants refer to Hanna et al., Ornfoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Appellants point to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on 08/20/04) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Appellants urge that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer still has a patentable utility in that it yields a more accurate tumor classification, relying upon the declaration by Dr. Ashkenzi (submitted under 37 C.F.R. § 1.132 on 08/20/04) and the Hanna et al. reference. Appellants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellants assert that the research community believes that the information obtained from these chips is useful. Finally, Appellants conclude that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO290 conveys utility to the claimed PRO290 polypeptides. This has been fully considered but is not found to be persuasive. Ornfoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Ornfoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Ornfoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO290 in the instant specification. That is, it is not clear whether or not PRO290 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Ornfoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on

large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability. Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al. and Chen et al. all speak to large sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in this answer. Regarding the Ashkenazi declaration, which will be further addressed below, and the Hanna et al. reference, the specification does not disclose that the PRO290 polypeptide levels increase **or** stay the same. Further research would be needed to determine PRO290 polypeptide levels in cancers showing gene amplification of PRO290 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO290 polypeptides as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides. The Hanna et al. reference actually supports the rejection, since Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes but not polypeptides. Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

From pages 5-6 of the Brief, Appellants take issue with the Hittelman et al., Haynes et al., Chen et al., Hu et al., Lian et al., and Fessler et al. references, stating that the references do not show a lack of correlation between mRNA and protein expression in general. Appellants urge that, while there may be exceptions, the central dogma of molecular biology is that there is a general correlation between DNA, mRNA, and protein levels. Appellants again refer to

Orntoft et al., Hyman et al., Pollack et al., and the Polakis declaration. Appellants urge that the art accepted use of array chips for detecting diagnostic markers lends further support that, in general, the skilled artisan would reasonably expect that the gene amplification data for the PRO290 gene indicates that the PRO290 polypeptide is overexpressed in lung and colon cancer and useful for the diagnosis of such. This has been fully considered but is not found to be persuasive. It is maintained that the Haynes et al., Chen et al., Hu et al., Lian et al., and Fessler et al. references support the rejection by establishing that it is not more likely than not that mRNA levels are predictive of protein levels. Orntoft et al., Hyman et al., Pollack et al., and Polakis declaration do not tip the balance of evidence in favor of Appellants' position. The merits of these pieces of evidence will be addressed below. Hittleman et al. deals with chromosomal instability and polysomy, not a correlation between the level of DNA and its encoded polypeptide. Therefore, Hittleman et al. does not support utility of the claimed polypeptide for the reasons previously set for in the rejection and as discussed in previously Office actions and here. Finally, the chips may provide useful information about genes, but not polypeptides. The skilled artisan recognizes this, and uses the chips to provide preliminary insight into which molecules may prove themselves useful as diagnostics upon further testing.

Appellants conclude (p. 7) that when the proper legal standard is applied, one reaches he conclusion that the present application discloses at least one patentable utility for the claimed PRO290 polypeptides. This has been fully considered but is not found to be persuasive, since the PRO290 polypeptide has no utility for the reasons set forth in the rejection under 35 U.S.C. § 101, it is also not enabled.

***Appellants' Response to Rejections***

**A. The legal standard for utility under 35 U.S.C. § 101**

At pp. 8-11 of the Brief, Appellants review the legal standard for utility.

Appellants argue (middle of p. 8) "that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use." This statement relates to the Court's decision in *Nelson v. Bowler.* In that decision, the CCPA says that specific therapeutic use of a compound is not necessary if there are

tests which evidence pharmacological activity of a compound. However, in this instance, pharmacological activity is not the same as gene amplification. In *Nelson,* the court held that the compound of which utility was in question, was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility. There are no test results to correlate the presence of PRO290 polypeptide with a diagnostic for lung or colon cancer. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:33 and utility as a cancer diagnostic. The findings of higher expression of the nucleic acid of SEQ ID NO:32 cannot be assumed to correlate to the higher expression of the encoded polypeptide in the same tissues.

On pages 8-9, Appellants also cite *Cross v. Iizuka* (Fed. Cir. 1985), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* amplification data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is whether genomic DNA levels correlated with encoded protein levels.

Appellants argue (pages 10) that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." While current availability of a claimed invention is not always necessary, the invention must still meet the requirements of 35 USC 101 and 112, first paragraph. For the reasons discussed here and in the previous Office actions, it is maintained the specification does not support utility, and the evidence submitted, including declarations, does not overcome the insufficiencies of the disclosure.

On pages 8-11, Appellants discuss credibility; however, credibility has not been raised as an issue.

**B. Proper application of the legal standard**

At p. 11 of the Brief, Appellants argue that the evidentiary standard to be used is the preponderance of the totality of the evidence. Appellants urge that the Examiner must establish that it is more likely than not that the skilled artisan would doubt the truth of the statement of utility. Appellants argue that the data in Example 170 (starting at p. 539 of the specification) describes results of a gene amplification assay. Appellants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellants assert that gene amplification is an essential mechanism for oncogene activation. Appellants review how the assay was performed, and reports that the gene encoding PRO290 was significantly amplified in several lung and colon tumors. This has been fully considered but is not found to be persuasive. The data pertaining to gene amplification do not convey utility to the claimed polypeptide, since amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al.).

On pages 12-13 of the Brief, Appellants refer to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 04 August 2005. Appellants quote from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellants conclude that one skilled in the art would consider the 2.97- to 4.2-fold amplification of the gene encoding PRO290 in lung and colon tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant

situation, the nature of the fact sought to be established is whether or not the amplification of the gene encoding PRO290 in lung and colon tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned relative to the *claimed* subject matter, namely, PRO290 *polypeptides*. Hu et al. and Chen et al. speak to the strength of the opposing evidence, as do Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al., discussed in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al., cited in the declaration of Dr. Goddard, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed in the rejection above. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO290 gene has *not* been associated with tumor *formation* or the *development* of cancer, nor has it been shown to be predictive of such. Similarly, the PRO290 gene has *not* been shown to be useful to track the *efficacy of cancer therapy*. The specification merely demonstrates that the PRO290 genomic DNA is amplified in some lung and colon cancers compared to normal DNA from blood. No mutation or translocation of PRO290 has been associated with any type of cancer versus normal tissue. It is not known whether PRO290 mRNA or polypeptide, as claimed, are elevated in any cancerous tissue. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO290 is amplified in a variety of samples and invites the artisan to determine the significance of this increase relative to the claimed subject matter. It remains that, as evidenced by the references of record, the issue is simply not predictable, and the specification presents a mere invitation to experiment. Based on consideration of the preponderance of the totality of the evidence as a whole, the rejection is proper.

**C. Appellants argue that a *prima facie* case of lack of utility has not been established**

Appellants on p. 14 argue that the PRO290 gene is useful as a biomarker even if the observed gene amplification was due to aneuploidy, and this use is supported by Sen. Because it

is the PRO290 polypeptide and not the gene which is claimed, even if the reported amplification of the nucleic acid of SEQ ID NO:32 were due to aneuploidy, this does not support a diagnostic utility for the encoded polypeptide or antibody for the reasons previously discussed.

On pages 14-15, Appellants argue that Hittleman et al. and the state of the art show detection of cancers using genes, and thus support utility for the PRO290 polynucleotide. The argument has been fully considered, but is not persuasive. The polynucleotide is not what is being claimed. Hittleman et al. deals with chromosomal instability and polysomy, not a correlation between the level of DNA and its encoded polypeptide. Therefore, Hittleman does not support utility of the claimed polypeptide for the reasons previously set for in the rejection and as discussed in previously Office actions and here. Further research would be needed to determine PRO290 polypeptide levels in cancers showing gene amplification of PRO290 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide levels (*e.g.,* Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al.).

Appellants take issue (pages 16-17) with the Pennica et al. and Konopka et al. references relied upon by the Examiner. Specifically, Appellants characterize Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Appellants point out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Appellants characterize Konopka et al. as being limited to the abl gene, and not speaking to genes in general. Appellants conclude that the Examiner must show evidence that it is more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Haynes et al., Gygi

et al., Lian et al., Fessler et al., Hu et al., Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding levels of PRO290 mRNA levels or PRO290 polypeptide levels in cancerous tissue. Finally, Pennica et al. provide evidence that closely related WISP genes show unpredictable gene amplification, mRNA, and polypeptide levels.

At p. 17 of the Brief, Appellants argue that Haynes et al. support Appellants' position when they state that there was a general trend between protein expression and transcript levels. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general.

From pages 17-18 of the Brief, Appellants criticize the Hu et al. reference. Specifically, Appellants criticize Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Appellants characterize Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Appellants criticize the types of statistical tests performed by Hu et al. Appellants conclude that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the Examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between

expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO290 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO290 protein can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO290 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304), and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO290 mRNA or polypeptide is overexpressed in cancer, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Appellants' criticism of Hu et al.'s statistical analysis, Appellant is holding Hu et al. to a higher standard than their own specification, which does not provide *any* statistical analysis such as reproducibility, standard error rates, etc. Regarding Appellants' criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At p. 19 of the Brief, Appellants argue that the Lian et al. publication is limited to differentiating myeloid cells and does not teach anything regarding a lack of correlation between mRNA levels and protein levels in general. Appellants also find fault with Lian et al. for using a relatively insensitive assay. This has been fully considered but is not found to be persuasive.

Lian et al. show a lack of correlation between mRNA levels and polypeptide levels in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels.") This is directly on point for the instant issue. Furthermore, Appellants again hold the reference to a higher standard than their own specification. Lian et al. used an art-accepted method to measure polypeptide levels whereas the instant specification and evidence of record do not report using any method to detect PRO290 polypeptide levels.

At pages 19-20 of the Brief, Appellants take issue with the Fessler et al. and Chen et al. publication, stating that Fessler et al. is limited to studying a few proteins/RNAs and both used an insensitive assay. Also, that Chen et al. support the position that it is more likely than not that an increase in gene amplification or mRNA elvels generally correlate well with increased protein levels. Appellants argue (page 28) that there are "limitations" in the technique used by Fessler et al., including possible artifactual transcript-protein discordance due to a 4 hour delay in harvesting after LPS exposure, uncertain post-incubation but pre-electorphoresis effects on protein synthesis, degranulation and exocytosis; and limited ability to quantitate protein amounts using Coomassie Blue (Fessler at 31301, left col.). The limitations of 2 D gel analysis are also pointed to. This has been fully considered but is not found to be persuasive because Fessler et al. found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract), which is directly on point regarding the instant issue. Furthermore, Appellants again hold the reference to a higher standard than their own specification. Fessler et al. and Chen et al. used an art-accepted method to measure polypeptide levels whereas the instant specification and evidence of record do not report using any method to detect PRO290 polypeptide levels. Fessler et al. attempted to limit problems associated with lowered sensitivity by using only those spots which were common to all twelve pH 3.0-10.0 two-D gels and which met statistical significance criteria (p. 31301 end of first full paragraph). The findings in general show that post-transcriptional and –translational modifications play an important role in biological influence of the encoding nucleic acid and encoded protein (*e.g.*, p. 31301, middle of last paragraph). It is concluded that (p. 31301, col. 2), "Although gene expression appears to be an important mechanism by which PMNs respond acutely to infection,

mRNA transcript/protein concordance is limited, and post-transcriptional (and post-translational) modifications also play an important role." The reference reinforces the complexity of translational factors and supports the warning concerning the inability to drawing conclusions about protein levels based on nucleic acid levels. While 2D gels might exclude low abundance proteins, their use is valid for detectable proteins. Chen et al. focused on those mRNA which encoded proteins that were detectable on 2D gels (p. 308, col. 2). The method was sensitive enough to determine that proteins having different isoforms also often had different protein/mRNA correlation coefficients (p. 309, paragraph bridging col. 1-2). It was concluded that absolute protein level did not influence the correlation with mRNA (p. 310, col. 1). Additionally, the correlation coefficient was not arbitrary chosen, but was based on detailed statistical analysis that resulted in those values above the assigned correlation coefficient to be considered significant if the designated difference was above the threshold (see paragraph bridging pages 307-308). The results of Chen et al. lead to the conclusion that post-translation modifications are likely to affect the correspondence (or lack thereof) of mRNA to protein levels (see Discussion). Chen et al. showed (p. 309, col. 2, 5$^{th}$ line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen et al. showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with their encoded proteins. 2D-PAGE is a common method of protein analysis and when the limitations are taken into account, as with Chen et al., the results are noteworthy.

At p. 20 of the Brief, Appellants argue that of the 66 genes with no isoforms shown by Chen et al., 40/66 had a positive correlation between mRNA and protein expression (Table 1). In Table II, which showed 30 genes with multiple isoforms, 22/30 showed a positive correlation between one isoform of each gene. No genes showed a negative isoform correlation. The argument has been fully considered, but is not persuasive. On page 309, first full sentence, Chen et al. state, "Among the 69 genes for which only a single protein spot was known (Table I), nine genes (9/69, 13%) were observed to show a statistically significant relationship between protein

and mRNA abundance..." Table I considered significance at $p<0.05$. It is unclear what Appellants are using as the criteria for positive correlation to determine that 40/66 genes showed a correlation. If the correlation is not significant, one cannot support presumptions concerning it. As to Table II, if one isoform out of, for example, three shows a correlation, that finding supports the unpredictability of mRNA/protein correlation levels. Contrary to Appellants' assertion that no genes showed a negative isoform correlation, α-1-Antitrypsin and PDI were shown to have such a negative isoform correlation. Further, a number of other proteins with isoform had some positive but insignificant correlations. Chen et al. is relied upon for teaching that assumptions cannot be made concerning mRNA/protein correlation with a reasonably certainty. The paper clearly answered the question posed: Does mRNA expression correlate with protein expression in lung tumor samples? The answer was 'no' in a majority of cases. This result directly supports the Examiner's finding that the art does not sustain a reasonable expectation that for any particular mRNA expressed in tumor, the amount of protein and encoding mRNA will correlate.

At page 21 of the Brief, Appellants argue that Hu et al., Lian et al., and Fessler et al. do not conclusively teach that, in general, protein levels cannot be accurately predicted from mRNA/gene amplification levels. Appellants argue that insensitive protein detection methods and methodology may have resulted in underrepresentation of certain protein species. Appellants urges that Haynes et al. and Chen et al. show a general positive correlation between increased gene amplification, mRNA and protein levels. Appellants conclude that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. In the instant case, the asserted utility that PRO290 polypeptide is useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for a PRO290 polypeptide to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO290 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (*e.g.*, Pennica et al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in healthy or diseased tissue (*e.g.*, Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding the levels of PRO290 polypeptide in cancerous tissues. In view of this, the skilled

artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO290 polypeptides can be used as a cancer diagnostic agent.

**D. Appellants argue that the gene amplification data establish a credible, specific, and substantial patentable utility for the claimed PRO290 polypeptide**

At pp. 21-22 of the Brief, Appellants argue that Example 170 states that amplification is associates with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers, and diagnostic determination of those cancers. Appellants urge that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer it is more likely than not that the encoded protein is overexpressed. Appellants point to Orntoft et al., Hyman et al., and Pollack et al. in support thereof. Specifically, Appellants characterize Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellants characterize Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellants characterize Pollack et al. as profiling DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Appellants conclude that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed

genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO290 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in colon or lung cancer.

In the paragraph bridging pages 22-23 of the Brief, Appellants refer to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 08/20/04. Appellants characterize the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellants conclude that all of the submitted evidence supports Appellants' position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO290 (i.e., data regarding amplification of PRO290 genomic DNA), and does not disclose any information regarding

PRO290 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, *e.g.,* Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), Haynes et al., Gygi et al., Lian et al., and Fessler et al., all discussed *supra.* (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the Assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the Examiner could not independently evaluate them. For example, how many of the tumors were lung or colon tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

At p. 23 of the Brief, Appellants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellant concludes that the research community believes that the information obtained from the chips is useful (i.e., that it is more likely than not that the results are informative of protein levels). This has been fully considered but is not found to be persuasive. Evidence of commercial success has no bearing on the issue of utility. The research community could just as easily be interested in the gene chips as a way of providing preliminary results, which would then be followed up with actual testing of protein levels.

On pages 23-24 of the Brief, Appellants conclude that the Examiner has disregarded the evidence provided in the referenced articles based on misinterpretations of their teachings. Appellants urge that the standard of "more likely than not" has been met by the disclosure, declarations, and references to establish that it is more likely than not that an amplified gene correlates with overexpressed protein. Appellants urge that the references used to support the rejection do not present a *prima facie* case of lack of utility. Appellants point to specific portions of the specification as supporting how to make and use the claimed polypeptide for lung or colon cancer diagnosis. Specifically, Appellants argue that the specification discloses the sequence of PRO290, including sequences comprising epitope tags of Fc regions, step-by-step protocols for making an expressing PRO290 in appropriate host cells, step-by-step protocols for production of antibodies that bind PRO290, and the gene amplification assay. Appellants conclude that the

skilled artisan would know how to make and use the claimed polypeptide for the diagnosis of lung or colon cancer. Appellant argues that, based on the disclosure and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not undue. This has been fully considered but is not found to be persuasive. The Examiner concedes that the specification teaches how to make PRO290 polypeptide. However, the specification fails to provide a substantial asserted utility for the claimed PRO290 polypeptide, and thus the specification also fails to enable the claimed PRO290 polypeptide (specifically, the specification fails to teach the skilled artisan how to use the claimed PRO290 polypeptides without undue experimentation). As discussed above, the PRO290 genomic DNA of SEQ ID NO: 32 was found to be amplified in lung and colon cancer samples. However, the literature reports that gene amplification does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). The literature also reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., Chen et al., Hanna et al.). These references particularly report that variant genes/proteins do not have the same patterns of amplification and overexpression (see especially Pennica et al. regarding the WISP genes and Hanna et al. regarding the HER-2 genes). In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO290 polypeptide is overexpressed in certain lung and colon tumors based on the disclosure regarding gene amplification for a single PRO290 gene (SEQ ID NO: 32) without actually testing for PRO290 polypeptide overexpression to reasonably confirm the specification's assertion that PRO290 is overexpressed in lung and colon tumors. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. In view of such, the asserted utility for PRO290 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this examiner's answer.

**(12) Oral Argument**

Appellants have not requested an oral hearing as of the date of this Examiner's Answer. However, if Appellants request an oral hearing, the examiner wishes to have the opportunity to present oral arguments.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Claire M. Kaufman, Ph. D
Patent Examiner, AU 1646

LORRAINE SPECTOR
PRIMARY EXAMINER

Conferees:

Janet Andres, Ph.D.

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

Gary Nickol, Ph.D.

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER